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CONFIDENTIAL AND PRIVILEGED
ATTORNEY CLIENT COMMUNICATION

## REMARKS/ARGUMENTS

In the Office Action dated November 18, 2003, all claims are rejected under 35 U.S.C. § 112, second paragraph and 35 U.S.C. § 103(a), and certain claims are rejected under 35 U.S.C. § 112, first paragraph, and under 35 U.S.C. § 102(b). Applicants respectfully request reconsideration of the rejections and further examination of the instant application in light of the foregoing amendments and the remarks and arguments which follow.

**Status of the Claims**

Claims 1-5, 7, 24-31 have been amended.

Claims 11-23 and 30-31 have been canceled.

Claim 9 stands withdrawn.

New claims 32-48 have been added.

Claims 1-8, 10 and 24-48 are currently pending.

**Amendment of the Specification**

The above-denoted paragraphs of the Specification have been amended to correct obvious typographical errors.

**Rejections Under 35 U.S.C. § 112, First Paragraph**

In the Office Action of November 18, 2003, claims 3 and 24-29 are rejected under 35 U.S.C. § 112, first paragraph, as failing to find enablement in the specification. In support thereof, the Office Action asserts that "... the most acidic calcium phosphate salt (as known in the art and taught by Applicants) only buffers in a range from about 6.2 to 8.2." This assertion is incorrect, however, as noted in paragraph 3 of the attached *Declaration of Dr. Kevin J. Thorne* (*e.g.*, showing an approximate buffering range of about pH 3.2 to 5.2 for monocalcium phosphate). Moreover, as described in the Brief Description of the Drawings and Example 1 of the specification, and shown in Figures 2-9, compositions containing an array of calcium phosphate salts were evaluated for ability to enhance explant mass, mineral mass, histology score and mineral concentration. As further discussed in Dr. Thorne's *Declaration*, one or more compositions containing acidic calcium phosphate salts produced surprisingly superior results for bone formation, particularly histological features such as bone maturation. The results were compared to the activity of control compositions containing collagen and bone proteins (Figures 2-5), or compared to control compositions containing collagen, bone protein and devitalized bone matrix (Figures 6-9). Figure 10 (histology score) and Figure 11 (relative mineral mass) show the performance of several acidic pH compositions (in the pH

range of 4.5 to 6.5) to which calcium and/or phosphate ions were added. Therefore, claims 3 and 24-29, as currently amended, are believed to fully comply with the requirements of 35 U.S.C. § 112, first paragraph.

**Rejections Under 35 U.S.C. § 112, Second Paragraph**

Claims 1-8, 10 and 24-29 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Although Applicants do not agree with the statement in the Office Action of November 18, 2003 that "...the skilled artisan would not know what a 'microenvironment' is" with respect to an implanted osteogenic device, in the interest of advancing prosecution, Applicants have canceled this language from the claims with the intention of refiling similar claims in a continuing application. Claims 1-8, 10 and 24-29, as currently amended on other grounds, are believed to fully comply with the requirements of 35 U.S.C. § 112, second paragraph.

**Rejections Under 35 U.S.C. § 102(b)**

In the Office Action of November 18, 2003, claims 1-5, 8, 10 and 24-27 stand rejected as being anticipated by *Ohura et al.* (1999). Applicants have amended claims 1-3 to require that the substrate comprises collagen, fibrin or alginate, or a mixture of any of those, and have amended claim 24 to require a collagen substrate. *Ohura et al.* does not teach the use of any of those substrate materials, and thus cannot anticipate claims 1-5, 8, 10 and 24-27.

**Rejections Under 35 U.S.C. § 103(a)**

Claims 1-8, 10 and 28-29 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over *Kwan et al.* in view of *Constantz* for reasons of record. It is said in the Office Action of November 18, 2003 that a combination of the composition taught by Kwan et al. and monocalcium monophosphate (MCMP) would have buffered the surface of the bone matrix to a pH of 6.2-8.2, especially absent convincing evidence to the contrary. Applicants respectfully traverse for at least the reason that an incorrect buffering range is imputed to calcium monophosphate, as supported by the attached Declaration of Dr. Kevin J. Thorne. Moreover, there is no teaching or suggestion in either of the cited references that the composition have an acidic pH capable of enhancing bone growth protein-induced bone formation when the composition is implanted in a mammal at a site in need of bone growth. Indeed, as detailed below, *Kwan et al.* and *Constantz* not only fail to teach or



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suggest this surprising feature of the claimed compositions, but instead are consistent with it being unexpected by one of skill in the art at the time invention.

**Unexpected Results**

The MPEP 716.01(a) provides that evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness, citing *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987). The MPEP 716.02(a) also provides that an absence of a property which a claimed invention would have been expected to possess based on the teachings of the prior art is evidence of unobviousness (citing *Ex parte Mead Johnson & Co.* 227 USPQ 78 (BPAI 1985)).

The Office Action of November 18, 2003 takes the position, that the only teachings in the specification are drawn to wherein calcium phosphate salts are added to a bone composition, and that this was old and known in the art. Applicants respectfully traverse, and submit that it was unexpected to one of ordinary skill in the art at the time Applicants' invention was made to make the composition acidic in pH to enhance bone growth protein induced bone formation.

Data showing unexpected properties of the claimed compositions are in the specification and drawings as filed. For example, increased explant mass (Figs. 2A,B and 6A,B), increased mineral mass (Figs. 5A,B and 9A,B), and markedly enhanced histology score or bone quality (Figs. 3A,B and 7A,B) are presented, and discussed at page 7, lines 3-5; page 11, lines 6-8, and page 13, lines 18-21) The *Declaration of Dr. Kevin J. Thorne* provides further evidence of unexpected results with respect to the claimed compositions. The Applicants' discovered that, surprisingly, pH plays a strong role in the osteogenic performance of compositions employing bone growth proteins, which was unexpected by those of skill in the art at the time of the invention. As discussed in the *Declaration of Dr. Kevin J. Thorne*, the skilled practitioner, at the time of the subject invention, would not have expected superior bone growth performance by a claimed acidic composition, compared to conventional or non-acidic bone growth compositions (*e.g.*, a hydroxyapatite composition with moderately alkaline pH or a calcium phosphate mixture at physiological pH).

The teachings of *Kwan et al.* represent the generally held belief of one of skill in the art at the time of the invention that a bone growth composition functions best *in vivo* at a neutral or slightly alkaline physiological pH (about 7.4). Indeed, at the time the present invention was made, the artisan of ordinary skill would be motivated by the teachings of *Kwan et al.* to adjust the pH of a calcium





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phosphate-containing collagen composition so as to ensure preservation of physiological conditions during the bone growth process with the idea of optimizing bone growth thereby. (See, *e.g.*, col. 3, lines 32-35 and col. 4, lines 27-29.) Although *Kwan et al.* provided a brief list of osteogenic materials (col. 5, lines 53-54), it is significant that there was no measurement or discussion of the impact or import of pH on their ability to induce bone growth, much less any report of enhanced efficacy. Moreover, it is noteworthy that bone marrow aspirate was included with their mineralized collagen matrix in Example II, but the pH of the matrix is neither mentioned nor demonstrated to enhance bone growth. By contrast, the compositions of claims 1-8, 10 and 28-29 require "an acidic pH capable of enhancing bone growth protein induced bone formation."

Similarly, although *Constantz* states that the particular mineral will be affected by the pH, and that the pH of the mixture will generally be in the range of about 5-8 (col. 4, l. 67 - col. 5, l. 2) or 5-9 (col. 5, l. 34-35), usually in the range of about 6-7.5 (col. 3, l. 13), the pH of the composition appears to merely reflect of the particular calcium/phosphate ratio employed to achieve the desired physical and mechanical properties of a composition (*e.g.*, flowable or formable, like clay). Admittedly, *Constantz* does independently recite certain pH ranges and list various proteins associated with the growth of bone (*e.g.* from cartilage, blood, dentin, bone and enamel). However, *Constantz* neither recognizes a relationship therebetween nor teaches anything about the enhancement of bone growth induced by any protein via a composition comprising an acidic pH. Indeed, in none of the four examples given does *Constantz* include bone growth protein or indicate the pH of the material.

As also noted in Dr. Thorne's *Declaration*, it is well known in the art that acidic implanted objects that reduce the physiological pH environment of the implantation site can cause undesirable effects. As summarized above and detailed in Dr. Thorne's *Declaration*, one of ordinary skill in the art would have been motivated to create compositions having a neutral or basic pH at the time of the claimed invention. Thus, one of skill in the art at the time of the invention would have been dissuaded from making bone growth protein containing compositions having sub-physiological pH. In contrast, Applicants' compositions of claims 1-8, 10 and 28-29 include an acidic pH and yet enhance bone growth protein induced bone formation when the composition is implanted at a site in need of bone growth.

For at least the foregoing reasons, claims 1-8, 10 and 28-29 are non-obvious over the combined teachings of *Kwan et al.* and *Constantz*.



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**Election/Restrictions**

Claims 30 and 31 were withdrawn in the Office Action as allegedly being directed to a non-elected invention. Applicants do not concede the correctness of this action, and do not waive the right to argue at another time in this or a continuing application that claims 30 and 31, as initially presented and as currently amended, are properly grouped with the bone growth composition claims of restriction Group I. Claims 30 and 31 are canceled.

**Additional Claim Amendments/New Claims**

Claims 4-6 have been amended to improve claim form or to better ensure coverage of embodiments to which Applicants are entitled, and which are supported in the specification and original claims.

Claim 7 is currently amended to omit duplication and to expressly recite a preferred embodiment. Collagen is supported in the specification in Example 1 at page 19, line 19, for example.

Claim 24 has been amended to require a collagen substrate and to recite a preferred pH range as specifically shown in Figures 10 and 11.

Claims 1-8, 10 and 24-29 have been amended to require that the composition comprises an acidic pH, or a pH within a stated acid range. Such amendments are supported throughout the specification; for example, at page 7, line 14 (acidic pH); and page 11, lines 12-13 (pH less than 7), and line 16 (pH 5 - 6.8), line 17 (pH 5.5 - 6.7), and Figures 10 and 11 (pH 4.5 - 6.5), and are drawn to embodiments to which Applicants are entitled.

New claims 32-43 depend from claim 1 or 24 and have been added to better ensure coverage of embodiments to which Applicants are entitled. The amendments are supported in the specification at page 12, lines 18-19 (claims 32 and 38); page 13, lines 1-2 (claims 33 and 39); page 15, lines 1-2 (claims 34 and 40); page 15, lines 2-3 (claims 35 and 41); page 15, lines 3-4 (claims 36 and 42); and page 15, lines 5-6 (claims 37 and 43).

New claim 44 depends from claim 1 and is drawn to a preferred embodiment as supported in the specification at page 18, line 22 to page 19, line 4, for instance.

New claims 45 and 46 depend from claims 2 and 3, respectively, and are drawn to a substrate specifically comprising collagen. These claims are supported in the claims as originally filed.

New claim 47 depends from claim 1 and is drawn to an acidic composition comprising a pH in the range of 4.5 to 6.5, as shown in Figs. 10 and 11, for example.



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New claim 48 depends from claim 1 and adds the further limitation of enhanced histologic score, as supported in the specification at page 12, lines 9-13 and page 14, lines 9-14, for example.

Each new claim depends from a claim of the elected restriction Group I, and are properly grouped with the original claims of that group. New claims 32-48 are patentable over the cited references for at least the same reasons as claim 1 or 24.

**Conclusion**

Applicants may have at times referred to claim limitations in shorthand fashion, or may have focused on a particular claim element. This discussion should not be interpreted to mean that the other limitations can be ignored or dismissed. The claims must be viewed as a whole, and each limitation of the claims must be considered when determining the patentability of the claims. Moreover, it should be understood that there may be other arguments with respect to patentability which have yet to be raised, but which may be raised in the future.

All of the pending claims are believed to be free of the prior art, and reconsideration and withdrawal of the rejections are respectfully requested. If a telephone conference would be helpful in advancing prosecution of this matter, the Examiner is invited to telephone the undersigned representative. Should any fees have been inadvertently omitted, or if any additional fees are required or have been overpaid, please appropriately charge or credit those fees to Deposit Account Number 03-2769 of Conley Rose, P.C., Houston, Texas, and consider this a petition for any necessary extension of time.

Respectfully submitted,

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